Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4567-4570, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00975-1

DEPHOSPHONYLATION OF α-FULLY SUBSTITUTED β-KETO PHOSPHONATES WITH $LiAlH_4$; REGIOSELECTIVE ALKYLATION OF KETONES EMPLOYING PHOSPHONATE AS A TEMPORARY ACTIVATING GROUP

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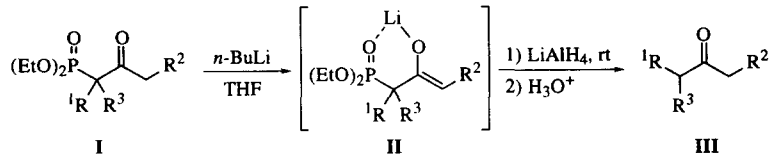
Abstract: Alkylation of β-keto phosphonates is performed by teatment of β-keto phosphonates with *n*-BuLi, followed by addition of alkyl halides. The acquired α-fully substituted β-keto phosphonates are dephosphonylated by treatment of the lithium enolates with $LiAlH_4$, followed by quenching with aqueous H_2SO_4 solution. This whole procedure represents a new route to regioselective alkylation of ketones.

β-Keto phosphonates[1] involve a phosphonate group as a regiocontrol element for the alkylation, such as β-keto esters[2] and β-keto sulfones[3] which are synthetically useful intermediates for preparation of regioselective α-substituted ketones by α-alkylation with subsequent defunctionalization. In contrast to the significant number of applications of β-keto esters and β-keto sulfones in this manner, the method using β-keto phosphonates has not been studied yet, due to the fact that dephosphonylation[4] of β-keto phosphonate is less known.

We reported recently, if the dephosphonylation of β-keto phosphonates bearing a hydrogen at the α-position is performed by succesive treatment with *n*-BuLi and $LiAlH_4$, then the corresponding ketones are obtained in good yields. In these cases, at least one hydrogen atom at the α-position of β-keto phosphonates was left unsubstituted for the enolate formation. The results suggested that reductive dephosphonylation with $LiAlH_4$ could occur *via* metal enolate of β-keto phosphonate.[5]

It was assumed that the α,α-disubstituted β-keto phosphonates **I** under similar conditions as described



I **II** **III**

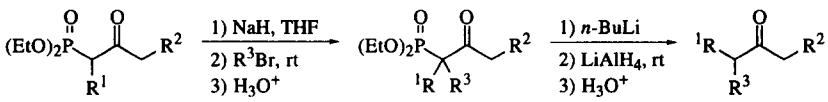
Scheme 1

above would provide the correspoding dephosphonylated ketones **III** *via* metal enolates **II** (Scheme 1). If successful, this approach would be well suited to the synthesis of ketones of the type **III** from the α,α-disubstituted β-keto phosphonates **I** by $LiAlH_4$-mediated reduction of presumed metal enolates **II** which in turn could be generated by treatment of **I** with *n*-BuLi.

First, we attempted alkylation of β-keto phosphonates[6] at the α-position for preparation of α-fully substituted β-keto phosphonates.[7] The reaction of sodium enolates of β-keto phosphonates with excessive alkyl halides at room temperature for 2-5 hours gave the corresponding α-fully substituted β-keto phosphonates in good yields without side products as shown in Table 1. Cyclic β-keto phosphonates required longer reaction time than acyclic ones. Use of excessive alkyl halides brought about short reaction time and yield-up, which are advantagements in comparison with but two literature examples[8] reported until now to our knowledge.

The acquired α-fully substituted β-keto phosphonates were dephosphonylated in the following manner[9]: *n*-BuLi was employded as a base, and the reaction of lithium enolates with $LiAlH_4$ at room temperature for 0.5-1 hours and then quenching with 5 N H_2SO_4 aqueous solution gave the corresponding

Table 1. Alkylation and Dephosphonylation of Substituted β-Keto Phosphonates



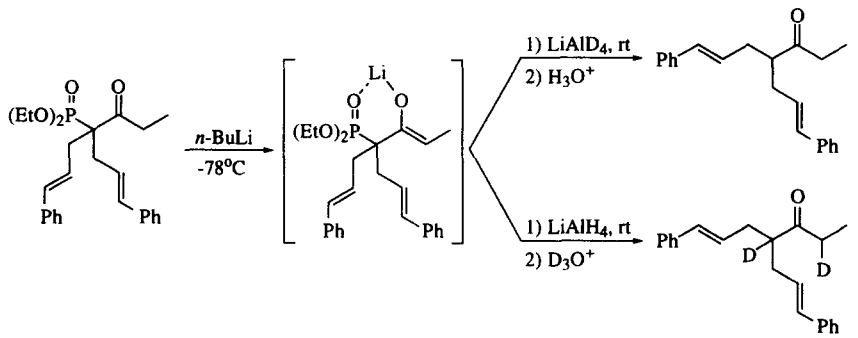
I **III**

entry	R^1	R^2	R^3	products **I** time(hr)	products **I** yield[a,b](%)	products **III** yield[a,b](%)
1	$-(CH_2)_2-$		cinnamyl	4	84	53 62[c]
2	$-(CH_2)_3-$		cinnamyl	4	74	46 72[c]
3	$-(CH_2)_3-$		allyl	5	67	58 66[c]
4	$-CH_2\underset{CH_3}{CH}CH_2-$		cinnamyl	5	72	88
5	Me	Et	crotyl	2	81	73[c]
6	Me	Et	cinnamyl	2	87	71
7	Me	H	crotyl	3	80	84
8	Me	H	cinnamyl	3	71	74
9	cinnamyl	Me	cinnamyl	3	74	77

[a]Yield of isolated, purified products. [b]Solvent was evaporated below 0°C. [c]LDA was used instead of *n*-BuLi as a base.

ketones in good yields along with a small amout of the corresponding alcohols resulting from overreduction as side products (Table 1). In some cases, improvement in yields was realized by the use of LDA instead of *n*-BuLi as a base.

To gain insight about the mechanism of dephosphonylation, we carried out the following reactions. When the reaction of lithium enolate of β-keto phosphonate with $LiAlD_4$ was followed by quenching with dilute H_2SO_4, product was the ketone containing no deuterium. In the case of using $LiAlH_4$ and deuterated acid, the reaction afforded the ketone[10] containing two deuteriums as shown in Scheme 2. These results suggest that the cleavage of the P-C bond is not caused by direct attack of hydride on the α-carbon atom linked with phosphorus atom or the γ-carbon atom as a S_N2' type reaction, and a possibility that acid might play a significant role in dephosphonylation.[11]



Scheme 2

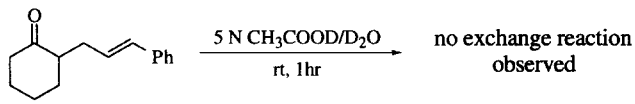
In conclusion, we have described the novel method for the preparation of regioselectively alkylated ketones. The whole procedure represents the use of β-keto phosphonates as precursors to regioselectively alkylated ketones. Further studies on the mechanism and dephosphonylation of other β-carbonyl phosphonates are in progress.

Acknowledgements : This research was supported by Korea Science and Engineering Foundation (KOSEF).

References and Notes

1. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738. Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499-2505. Horner, L.; Hoffmann, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber.* **1962**, *95*, 581-601. Wadworth, W. S. *Org. React. (N. Y.)* **1977**, *25*, 73-253.
2. Krapcho, A. P. *Synthesis* **1982**, 893-914.
3. Kinoshita, H.; Hori, I.; Oishi, T.; Ban, Y. *Chem. Lett.* **1984**, 1517-1520. Kurth, M. J.; O'brien, M. J. *J. Org. Chem.* **1985**, *50*, 3846-3848. Fujii, M.; Nakamura, K.; Mekata, H.; Oka, S.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 495-500.

4. To distinguish between "dephosphorylation" and "dephosphonylation", we use the term "dephosphonylation" as a limited meaning of P-C bond cleavage in compounds containing phosphonate groups.
5. Hong, J. E.; Shin. W. S.; Jang, W. B.; Oh, D. Y. *J. Org. Chem.* **1996**, *61*, 2199-2201.
6. Savignac, P.; Mathey, F. *Tetrahedron Lett.* **1976**, 2829-2832. An, Y. Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197-8202. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071-3072.
7. A typical procedure is as follows: β-Keto phosphonates were prepared according to their references. Phosphonate (diethyl 2-oxocyclopentylphosphonate, 0.44 g, 2.0 mmol) in dry THF (5 mL) was added slowly to the suspension of sodium hydride (0.060 g, 2.0 mmol) rinsed with hexane in dry THF (5 mL) under N_2 at 0 °C and the mixture was allowed to stir at room temperature for 1 h. Cinnamyl bromide (0.79 g, 4.0 mmol) in dry THF (5 mL) was added and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched by aqueous 3.5 N H_2SO_4 (5 mL) and the resulting solution extracted with diethyl ether (50 mL x 2). The combined organics were washed with 5 % $NaHCO_3$ (5 mL x 1), dried ($MgSO_4$) and evaporated. The pure alkylated 2-oxoalkylphosphonate was obtained using silica gel chromatography (EtOAc/hexane 50/50) as a colorless oil (diethyl 1-cinnamyl-2-oxocyclopentylphosphonate, 0.565 g, 1.68 mmol, 84 %).
8. Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis* **1975**, 635-636. Ruder, S. M.; Kulkani, V. R. *Synthesis* **1993**, 945-947.
9. A typical procedure is as follows: *n*-BuLi (0.69 mL of a 1.6 M in hexane, 1.1 mmol) or LDA (0.55 mL of a 2 M in heptane/THF/ethylbezene, 1.1 mmol) was added slowly by syringe to phosphonate (diethyl 1-cinnamy-2-oxocyclopentylphosphonate, 0.336 g, 1.00 mmol) in dry THF under N_2 at -78°C and then the reaction was allowed to warm slowly to room temperature. The resulting enolate was transferred into a stirred solution of $LiAlH_4$ (0.114 g, 3.0 mmol) in dry THF (6 mL) at room temperature and stirred for 30 min. The reaction was quenched by aqueous 5 N H_2SO_4 (5 mL) and the resulting solution extracted with diethyl ether (50 mL x 2). The combined organics were washed with 5% $NaHCO_3$ (5 mL x 1), dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (EtOAc/hexane 10/90) to give the corresponding alkylated ketone as a colorless oil (2-cinnamylcyclopentanone, 0.107 g, 0.534 mmol, 53 % for using *n*-BuLi as a base; 0.124 g, 0.619 mmol, 62 % for using LDA as a base).
10. To investigate the possibility of H-D exchange reaction between D_3O^+ and ketone, the blank experiment was carried out as follows. In result, no deuterized ketone was observed, which confirms the fact that the proton exchange reaction of the product ketones don't take place under our quenching conditions.



11. In quenching, use of more dilute H_2SO_4 aqueous solution brought about reduced yields. This result gives a little support for the possibility that acid might play a significant role in P-C bond cleavage.

(*Received in Japan* 10 *March* 1997; *accepted* 13 *May* 1997)